1 ICH E3 COMPLIANT SYNOPSIS (9463-CL-1302 / FG-463-21-20)

Name of Sponsor / Company: Astellas Pharma Europe B.V.		
Name of Finished Product: Micafungin (Mycamine®)		
Name of Active Ingredient: FK463		
Title of Study: A phase II, multicentre, randomised, open-label, active controlled study to evaluate the efficacy and safety of micafungin salvage mono therapy versus active control intravenous salvage mono therapy in patients with invasive aspergillosis.		
Responsible Medical Officer / Coordinating Investigator: [redacted] / N.A.		
Investigators: [redacted] (BE), [redacted] (FR), [redacted] (SP), [redacted] (IT), [redacted] (HU), [redacted] (BR), [redacted] (DE), [redacted] (CZ), [redacted] (CZ).		
Study Centers: In total 9 (out of 63) sites from 8 (out of 12) countries randomized subjects in the study: eight centers from seven (out of nine) European countries (Belgium [BE], Czech Republic [CZ], France [FR], Germany [DE], Hungary [HU], Italy [IT] and Spain [SP]) and one (out of three Latin American centers) from Brazil [BR].		
Publication (reference): None		
Study Period: **Date of First Enrollment:** 30 June 2006 **Date of Last Evaluation:** 7 September 2008		**Phase of Development: II**
Objectives: To evaluate the efficacy and safety of micafungin in subjects with proven (probable only in case of pulmonary aspergillosis) invasive aspergillosis and who were also refractory or intolerant to previous systemic antifungal therapy. To compare the efficacy and safety of the micafungin therapy arm with the active control arm.		
Study Design: Phase II, multicenter, prospective, active controlled, open-label, 2:1 randomized and parallel group clinical study. Subjects were stratified according to baseline infection and neutropenic status. Subjects (18 years or older with proven invasive aspergillosis) received either 300 mg/day intravenous (i.v.) micafungin mono therapy or an active control i.v. salvage mono therapy (amphotericin B either liposomal, colloidal dispersion or lipid complex, voriconazole or caspofungin) for 3 to 12 weeks. The end of study (EoS) was 12 weeks post-treatment.		
Diagnosis and Main Criteria for Inclusion: Subjects, 18 years or older with allogeneic or autologous haematopoietic stem cell transplantation (HSCT), acute leukaemia, myelodysplastic syndrome (MDS), with proven (probable only in case of pulmonary aspergillosis) invasive aspergillosis and who were also refractory to at least 7 consecutive days of a systemic antifungal agent used as first line therapy, or intolerant to at least one dose of a systemic antifungal agent.		
Number of Subjects (planned and analyzed): The planned primary set for efficacy according the protocol contained 120 evaluable subjects; 80 in the micafungin and 40 in the active control drug arm. The study was stopped prematurely due to mismatch of the existing inclusion criteria in the protocol (requiring monotherapy) with the (changed) current use of combination therapy in the setting of salvage therapy, resulting in a low enrollment (n=17).		
Test Product, Dose And Mode of Administration: Subjects were randomized to either a) micafungin of 300 mg/day as investigational drug, or b) liposomal, colloidal dispersion or lipid complex amphotericin B (all 5 mg/kg/day), voriconazole		

(8 mg/kg/day with 12 mg/kg/day as loading dose) or caspofungin (50 mg/day with 70 mg/day as loading dose) as control drugs. All drugs were administered intravenously: 1 h for micafungin; doses and infusion rate of the active control drugs according instruction of manufacturer.

Lot Numbers:
Micafungin (FK463) 50 mg dry powder for solution of infusion: [redacted].
Control drugs were ordered and supplied by the sites to the subjects as commercially available drug.

Duration of Study and Treatment:
Study drug was to be administered during the treatment period for a minimum of 3 weeks and up to 12 weeks. The post treatment period was to be 12 weeks for every subject. The maximum study duration for a subject was 24 weeks.

Criteria for Evaluation:
Due to premature termination of the study, originally planned analyses could not be performed with the exception of overall success (see Statistical Methods). The reported criteria for evaluation are based on the updated Statistical Analysis Plan instead of the protocol.
Primary endpoint: Independent Data Review Board (IDRB) assessment of the overall success at the end of treatment (EoT) defined as yes or no. The assessment of clinical response was based on clinical signs and symptoms and radiological findings. The IDRB was blinded to the treatment group.
Major secondary efficacy endpoints were:

- Overall success at 12 weeks after Day 1 (yes or no) as assessed by the IDRB, and at EoT and 12 weeks after Day 1 by the investigator, all by treatment arm.
- Clinical response (complete, partial, stable response, failure) at EoT, at 12 weeks after Day 1 and at EoS as assessed by the IDRB and by the investigator

Major secondary safety endpoints were:

- Mycological response (eradication, presumed eradication, persistence, not applicable) at EoT, 12 weeks after Day 1 and EoS as assessed by the IDRB
- Overall incidence of treatment emergent AEs and SAEs
- Summary of deaths and relationship to invasive aspergillosis as assessed by IDRB

After evaluation of all scans by the IDRB's radiologist, the three clinical IDRB experts evaluated all clinical and radiological data blindly and independent from each other. A univocal agreement was obtained by discussing any differences in data evaluated during three teleconferences. All presented results were obtained from the full analysis set (FAS). The FAS consisted of all randomized subjects who received at least one dose of randomized study drug.
Before the analysis, the IDRB proposed to use newly defined clinical response criteria. IDRB's criteria are only presented if different from the protocol criteria. The protocol and IDRB's new proposal are presented in the IDRB charter and Table 1:

Table 1: Clinical response according to protocol and new IDRB defined criteria

Clinical response	
According Protocol (App. IV)	**According IDRB proposal**
CR: ≥ 90% improvement	CR: ≥ 90% improvement
PR: ≥ 50% but < 90% improvement	IR: ≥ 30% but < 90% improvement
SR: 0 - < 50% improvement	S: between > -20% deterioration and < 30% improvement
PD: < 0% is progressive disease	F: ≤ - 20% deterioration is progressive disease

CR: Complete response; PR: Partial response; IR: Incomplete response; SR: Stable response; S: Stable; PD: Failure Progression disease; F: Failure.

Statistical Methods:
As the planned primary objective focuses on the efficacy and safety of subjects treated with micafungin,

a formal statistical sample size calculation for the comparison between the two treatment groups was not performed. The originally planned sample size of 120 evaluable subjects (about 80 subjects in the micafungin treatment group and 40 subjects in the control group) was chosen based on feasibility (number of subjects eligible and length of time for recruitment) and on the assumed difference between the lower limit of a confidence interval for the observed success rate and the true success rate in the micafungin treatment group.
The sample size of 120 subjects, using a 2:1 randomization scheme, was based on the Modified Full Analysis Set (MFAS) according to IDRB assessment. It was assumed that in total a minimum of 135 subjects would be randomized to achieve 120 subjects in this analysis set. In the literature response rates in the salvage treatment of invasive aspergillosis vary between 36% and 48%.

The Pharmacokinetics Analysis Set (PKAS) included the subjects from the Safety Analysis Set (SAF) who were enrolled in the PK sub-study and for whom sufficient plasma concentration data were available to facilitate derivation of at least one PK parameter. Subjects or specific time points might have been excluded from the PKAS at the discretion of the pharmacokineticist. In addition, the PKAS would also included the subjects from the study for whom samples were collected to determine micafungin and metabolite concentrations. These samples were included in all tables and graphical summaries of the PK data. Formal definitions for exclusion of subjects from the PKAS were determined prior to or during the BDRM, if needed, and were documented in the minutes. The PKAS was used for all tables and graphical summaries of the PK data

As a consequence of the premature stop of the study with the small number of subjects descriptive statistical analysis has been performed only on the FAS. An exploratory analysis was only performed on overall success.

RESULTS:
Analysis Sets and Subject Disposition:

Seventeen subjects were randomized either to micafungin (n=12) or the active control (n=5). The active control group were treated with either caspofungin (n=4) or voriconazole (n=1).
Of the 17 subjects enrolled, seven (41.2%) (four in the micafungin group) completed therapy and 10 (58.8%) (eight in the micafungin group) prematurely discontinued from therapy. A total of six subjects completed the study up to the 12-week post-treatment period and 11 subjects discontinued the study prior to the 12-week post-treatment visit.
During the course of the study 11 subjects died. Adverse events are summarized and listed by MedDRA 5.0 system organ class and preferred term. Subject disposition is presented in Table 2.

Table 2: Subject disposition

Completion/discontinuation	Micafungin (N=12)		Active Control (N=5)		Total (N=17)	
	N	(%)	N	(%)	N	(%)
Completing Treatment	4	(33.3%)	3	(60.0%)	7	(41.2%)
Discontinued from Study in post-treatment period	1	(8.3%)	2	(40.0%)	3	(17.6%)
Completing Study	3	(25.0%)	1	(20.0%)	4	(23.5%)
Discontinued from Treatment	8	(66.7%)	2	(40.0%)	10	(58.8%)
Discontinued from Study at same time	1	(8.3%)	1	(20.0%)	2	(11.8%)
Discontinued from Study at a later time	5	(41.7%)	1	(20.0%)	6	(35.3%)
Completing Study	2	(16.7%)	0		2	(11.8%)

Source: Table 12.1.2.

Demographics:
Demographic data such as age, weight, and height, gender and race are comparable between the two treatment groups, and is presented in Table 3.

Table 3: Subject demographics

Demographics	Micafungin (N=12)		Active Control (N=5)		Total (N=17)	
Age (years)						
Mean (range)	54.1 (28 – 76)		52.4 (25 – 69)		53.6 (25 – 76)	
SD	12.39		16.43		13.18	
Weight (kg)						
Mean (range)	68.0 (45 – 85)		69.6 (50 – 80)		68.5 (45 – 85)	
SD	12.75		11.52		12.06	
Height (cm)						
Mean (range)	173.6 (157 – 191)		172.6 (167 – 178)		173.3 (157 – 191)	
SD	11.22		5.27		9.68	
Sex	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
Male	7	(58.3%)	4	(80.0%)	11	(64.7%)
Female	5	(41.7%)	1	(20.0%)	6	(35.3%)
Race						
White	10	(83.3%)	5	(100%)	15	(88.2%)
Black	2	(16.7%)	0		2	(11.8%)

Source: Table 12.1.3.1.

Baseline Characteristics:
Subjects were stratified according to baseline neutropenic (absolute neutrophil count [ANC] < 500 cells/mm³) status (see Table 4). Baseline infection status is given by investigator (Table 5) and IDRB (Table 6).

Table 4: Baseline stratification factors

	Baseline infection status							
Study drug Baseline neutropenic status	**Intolerant**		**Refractory Progression of Infection**		**Refractory Failure to Improvement**		**Total**	
	N	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
Micafungin								
Total	2	(100.0%)	3	(100.0%)	7	(100.0%)	12	(100.0%)
Neutropenic	1	(50.0%)	2	(66.7%)	3	(42.9%)	6	(50.0%)
Non-Neutropenic	1	(50.0%)	1	(33.3%)	4	(57.1%)	6	(50.0%)
Active control								
Total			4	(100.0%)	1	(100.0%)	5	(100.0%)
Neutropenic			3	(75.0%)	0		3	(60.0%)
Non-Neutropenic			1	(25.0%)	1	(100.0%)	2	(40.0%)

Source: Table 12.1.3.2.

Table 5: Assessment of invasive fungal infection at baseline by investigator

	Micafungin (N=12)		**Active Control (N=5)**		**Total (N=17)**	
	N	**(%)**	**N**	**(%)**	**N**	**(%)**
Type of Invasive Infection:						
Pulmonary	11	(100.0%)	5	(100.0%)	16	(100.0%)
Proven	1	(9.1%)	0		1	(6.3%)
Probable	10	(90.9%)	5	(100.0%)	15	(93.8%)
No invasive infection	1*		0		1	
Mycological documentation	11	(100.0%)	4	(100.0%)	15	(100.0%)
Aspergillus sp. identified	2	(18.2%)	1	(25.0%)	3	(20.0%)
Aspergillus sp. (not identified)	6	(54.5%)	2	(50.0%)	8	(53.3%)
Unknown/no organism cultivated	3	(27.3%)	1	(25.0%)	4	(26.7%)
No mycology	1*		1		2	
Method of diagnosis	11	(100.0%)	5	(100.0%)	16	(100.0%)
Galactomannan	8	(72.7%)	4	(80.0%)	12	(75.0%)
Histology (only)	1	(9.1%)	0		1	(6.3%)
Fungal culture (only)	2	(18.2%)	1	(20.0%)	3	(18.8%)
Not recorded	1		0		1	
Invasive Aspergillus Infection:	11	(100.0%)	5	(100.0%)	16	(100.0%)
Not Confirmed	3	(27.3%)	2	(40.0%)	5	(31.3%)
Confirmed	8	(72.7%)	3	(60.0%)	11	(68.8%)
Not Recorded	1*		0		1*	

Source: Tables 12.1.3.7 and 12.1.3.8, and Listing 13.2.4.2.
*One subject ([redacted]) does not have aspergillosis.

Table 6: Assessment of invasive fungal infection at baseline by IDRB

	Micafungin (N=12)		Active Control (N=5)		Total (N=17)	
	N	(%)	N	(%)	N	(%)
Type of Invasive Infection:						
Pulmonary	11	(100.0%)	5	(100.0%)	16	(100.0%)
Proven	2	(18.2%)	0		2	(12.5%)
Probable	9	(81.8%)	5	(100.0%)	14	(87.5%)
No mycology, no aspergillosis	1*		0		1	
Mycological documentation	11	(100.0%)	5	(100.0%)	16	(100.0%)
Aspergillus sp. identified	1	(9.1%)	1	(20.0%)	2	(12.5%)
Aspergillus sp. (not identified)	3	(27.3%)	0		3	(18.8%)
Galactomannan only	6	(54.5%)	4	(80.0%)	10	(62.5%)
Mould	1	(9.1%)	0		1	(6.3%)
No mycology	1*		0		1	

Source: Tables 12.1.3.11 and 12.1.3.13, and Listings 13.2.4.3 and 13.2.4.4.
*One subject ([redacted]) does not have aspergillosis.

The following organisms were identified in the micafungin/active control group as assessed by the IDRB: *Aspergillus* species (not specified): 3/0; *Aspergillus fumigatus*: 1/1; *Aspergillus flavus*: 1/0; Other organism of infection: 7/4, from which galactomannan was identified in 10 out of 11 cases.
The CT scan was mainly used (in 15 out of 17 subjects) versus X-ray only in one subject in each group.
The IDRB assessed acute myelogenous leukemia as the most reported primary underlying disease (66.7% versus 80.0% for micafungin and active control, respectively).

Study Drug Exposure:
The treatment duration was minimal 4 days and maximal 64 days with a median of 10 days (mean of 15.8; range 4-34) for micafungin and 18 days (mean of 27.4; range 10-64) for the active control group. The average daily dose was 300 mg (mean 4.6 mg/kg) for micafungin (n=12), 51.0 mg (mean 0.8 mg/kg) for caspofungin (n=4) and 516 mg (mean 7.4 mg/kg) for the single voriconazole treated subject. The total study duration was minimal 5 days and maximal 119 days after randomization.
Pharmacokinetic results:
Plasma trough levels of micafungin have been obtained and analyzed from 11 out of 12 subjects at Day 2, Day 15 and EoT (Table 7).

Table 7: Micafungin trough levels by visit by FAS

	Micafungin (µg/mL) (N=11)					
Visit	**N**	**Mean**	**SD**	**Min**	**Median**	**Max**
Day 2	9	4.5	2.5	1.3	4.4	10.5
Day 15	2	15.2	6.4	10.7	15.2	19.7
EoT	4	19.4	26.9	0.5	9.0	59.1

Source: Table 12.4.1 and Listing 13.2.5.3.1.
FAS: full analysis set; EoT: end of treatment.

Efficacy Results:
Primary endpoint:
The IDRB assessed overall treatment success at EoT as primary efficacy endpoint from the FAS dataset is presented in Table 8. Three subjects in each group had a successful therapy at the end of the study

drug treatment. The small number of subjects induces a wide range in the confidence interval, limiting the ability to draw any statistical conclusion about the study outcome.
There is no difference in this primary outcome between the protocol and new IDRB defined criteria.

Table 8: IDRB overall treatment success at end of treatment (EoT)

Full Analysis Set (FAS) at end of treatment (EoT)	Micafungin 300 mg (N=12)		Active Control (N=5)	
	N	(%)	N	(%)
Successful therapy	3	(25.0%)	3	(60.0%)
95% CI	[5.5%, 57.2%]		[14.7%, 94.7%]	
Difference (Micafungin – Active Control)	-35.0%			
95% CI for difference	[-72.7%, 14.4%]			

Source: Tables 12.3.1 and 12.3.2.
CI: confidence interval.

Secondary efficacy endpoints:
The IDRB assessed secondary efficacy endpoints were the overall treatment success at 12 weeks after Day 1 (Table 9), the clinical response at EoT, 12 weeks after Day 1 and EoS (Table 10), and mycological response (Table 11).

Six subjects in the micafungin group and one in the active control group showed a successful therapy 12 weeks after start of therapy. Three subjects showed a positive clinical response in the micafungin group versus one in the active control group after the end of study.
There are no differences in these secondary outcome parameters between the protocol and new IDRB defined criteria.
The evaluations by the investigators differ slightly from those from the IDRB. All their evaluations are presented in the final tables as shown in the attachments.

Table 9: IDRB overall treatment success at 12 weeks after Day 1

FAS at 12 Weeks after Day 1	Micafungin (N=7)		Active Control (N=2)	
	N	(%)	N	(%)
Successful Therapy	6	(50.0%)	1	(20.0%)
95% CI	[21.1% , 78.9%]		[0.5% , 71.6%]	
Difference (Micafungin – Active Control)	30.0%			
95% CI for difference	[-22.8% , 65.9%]			
Not recorded	6	50.0%	4	80.0%

Source: Table 12.3.4.
CI: confidence interval; FAS: full analysis set.

Table 10: IDRB Clinical response at EoT, 12 weeks after Day 1 and EoS

Clinical Response (FAS)	Micafungin (N=12)		[95% CI]	Active Control (N=5)		[95% CI]
Visit	**N**	**(%)**		**N**	**(%)**	
End of treatment (EoT)	12	(100.0%)		5	(100.0%)	
Response	3	(25.0%)	[5.5% , 57.2%]	3	(60.0%)	[14.7% , 94.7%]
Complete	1	(8.3%)		1	(20.0%)	
Partial	2	(16.7%)		2	(40.0%)	
No Response	9	(75.0%)		2	(40.0%)	
Stabilization	3	(25.0%)		0		
Failure	6	(50.0%)		2	(40.0%)	
12 weeks after Day 1	12	(100.0%)		5	(100.0%)	
Response	5	(41.7%)	[15.2% , 72.3%]	1	(20.0%)	[0.5% , 71.6%]
Complete	3	(25.0%)		1	(20.0%)	
Partial	2	(16.7%)		0		
No response	7	(58.3%)		4	(80.0%)	
Not Assessed	2	(16.7%)		1	(20.0%)	
Missing	5	(41.7%)		3	(60.0%)	
End of study (EoS)	12	(100.0%)		5	(100.0%)	
Response	3	(25.0%)	[5.5% , 57.2%]	1	(20.0%)	[0.5% , 71.6%]
Complete	2	(16.7%)		1	(20.0%)	
Partial	1	(8.3%)		0		
No response	9	(75.0%)		4	(80.0%)	
Not Assessed	3	(25.0%)		1	(20.0%)	
Missing	6	(50.0%)		3	(60.0%)	

Source: Table 12.3.7.
CI: confidence interval; FAS: full analysis set; EoT: end of treatment; EoS: end of study.

Table 11: IDRB mycological response at EoT, 12 weeks after Day 1 and EoS

Mycological Response (FAS)	Micafungin (N=12)		[95% CI]	Active Control (N=5)		[95% CI]
Visit	**N**	**(%)**		**N**	**(%)**	
End of treatment	12	(100.0%)		5	(100.0%)	
Success	2	(16.7%)	[2.1% , 48.4%]	3	(60.0%)	[14.7% , 94.7%]
Eradication	1	(8.3%)		2	(40.0%)	
Presumed eradication	1	(8.3%)		1	(20.0%)	
Failure	10	(83.3%)		2	(40.0%)	
Persistence	5	(41.7%)		2	(40.0%)	
Not Assessed	5	(41.7%)		0		
12 weeks after Day 1	12	(100.0%)		5	(100.0%)	
Success	4	(33.3%)	[9.9% , 65.1%]	1	(20.0%)	[0.5% , 71.6%]
Eradication	1	(8.3%)		0		
Presumed eradication	3	(25.0%)		1	(20.0%)	
Failure	8	(66.7%)		4	(80.0%)	
Persistence	1	(8.3%)		0		
Not Assessed	7	(58.3%)		4	(80.0%)	

ISN 9463-CL-1302
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Mycological Response (FAS)	Micafungin (N=12)		[95% CI]	Active Control (N=5)		[95% CI]
Visit	**N**	**(%)**		**N**	**(%)**	
End of study	12	(100.0%)		5	(100.0%)	
Success	2	(16.7%)	[2.1% , 48.4%]	1	(20.0%)	[0.5% , 71.6%]
Eradication	1	(8.3%)		0		
Presumed eradication	1	(8.3%)		1	(20.0%)	
Failure	10	(83.3%)		4	(80.0%)	
Persistence	1	(8.3%)		0		
Not Assessed	9	(75.0%)		4	(80.0%)	

Source: Table 12.3.9.
CI: confidence interval; FAS: full analysis set; EoT: end of treatment; EoS: end of study.

Safety Results:
In total 11 subjects died during the study: five during treatment (three in micafungin group [25%] and two in the active control group [40%]), and six in the post-treatment period (four in the micafungin group [33.3%] and two in the active control group [40%]). Infections, and respiratory, blood and general disorders were the causes of death. Further details of the deaths and SAEs are provided in Table 14.

An overall summary of (serious) adverse events is presented in Table 12. Overall treatment emergent serious adverse events are presented in Table 13. Adverse events reported by two subjects or more per treatment are leukocytosis, neutropenia, melaena, nausea, chest pain and sepsis, and presented by preferred terms (MedDRA 5.0) in Table 14. Narratives from in total 13 subjects who experienced SAEs are presented in the attachments.

Table 12: Overall treatment emergent adverse events by FAS

Total events	Micafungin (N=12)			Active Control (N=5)			Total (N=17)		
	Subjects		Events	Subjects		Events	Subjects		Events
	N	(%)	N	N	(%)	N	N	(%)	N
Adverse Events	10	(83.3%)	36	5	(100.0%)	29	15	(88.2%)	65
Serious Adverse Events	5	(41.7%)	7	4	(80.0%)	8	9	(52.9%)	15
Causally-related AE*	3	(25.0%)	4	1	(20.0%)	1	4	(23.5%)	5
Serious Causally-related AEs*	0		0	1	(20.0%)	1	1	(5.9%)	1

Source: Table 12.6.1.1
FAS: full analysis set; AE: adverse event.
Within a system organ class, subjects may have reported more than one type of adverse event. An adverse event observed after starting administration of the test drug/comparative drug is called "treatment emergent adverse event".
* Causally-related is defined as probable, possible or missing relationship with study drug as assessed by the investigator.

Table 13: Treatment emergent serious adverse events by preferred term by treatment

Treatment emergent SAE (FAS)	Micafungin (N=12)	Voriconazole (N=1)	Caspofungin (N=4)	Total (N=17)
Preferred term (MedDRA 5.0) by treatment	**(N=5)**	**(N=1)**	**(N=3)**	**(N=9)**
Total events	7	2	6	15
Oxygen saturation decreased	1			1
Respiratory failure	1			1
Leukaemia NOS	1			1
Bronchopulmonary aspergillosis	1			1
Dyspnoea NOS	1			1
Oesophageal candidiasis	1			1
Melaena	1			1
Septic shock		1		1
Respiratory distress		1		1
Pyrexia			1	1
Sepsis NOS			2	2
Cholestasis			1	1
Multiorgan failure			1	1
Abdominal pain NOS			1	1

Source: Listing 13.2.7.2. Incidence of any treatment emergent SAE is reported per treatment group.
FAS: full analysis set; SAE: serious adverse event; NOS: not otherwise specified.
Within a system organ class, subjects may have reported more than one type of adverse event. An adverse event observed after starting administration of the test drug/comparative drug is called "treatment emergent adverse event".

Table 14: Overall incidence of treatment emergent adverse events by system organ class, and preferred terms regardless of relationship to study drug by FAS

Adverse events	Micafungin (N=12)			Active Control (N=5)			Total (N=17)		
	Subjects		Events	Subjects		Events	Subjects		Events
System Organ Class Preferred Term	**N**	**(%)**	**N**	**N**	**(%)**	**N**	**N**	**(%)**	**N**
Blood and lymphatic system disorders	**5**	**41.7%)**	**6**	**1**	**(20.0%)**	**1**	**6**	**(35.3%)**	**7**
Leukocytosis	2	(16.7%)	2	0		0	2	(11.8%)	2
Neutropenia	2	(16.7%)	2	0		0	2	(11.8%)	2
Anemia NOS	1	(8.3%)	1	0		0	1	(5.9%)	1
Splenomegaly	0		0	1	(20.0%)	1	1	(5.9%)	1
Thrombocytopenia	1	(8.3%)	1	0		0	1	(5.9%)	1
Gastrointestinal disorders	**4**	**33.3%)**	**8**	**2**	**(40.0%)**	**2**	**6**	**(35.3%)**	**10**
Diarrhea NOS	1	(8.3%)	1	1	(20.0%)	1	2	(11.8%)	2
Melaena	2	(16.7%)	2	0		0	2	(11.8%)	2
Nausea	2	(16.7%)	2	0		0	2	(11.8%)	2
Abdominal pain NOS	0		0	1	(20.0%)	1	1	(5.9%)	1
Constipation	1	(8.3%)	1	0		0	1	(5.9%)	1
Gingival bleeding	1	(8.3%)	1	0		0	1	(5.9%)	1
Vomiting NOS	1	(8.3%)	1	0		0	1	(5.9%)	1

Adverse events	Micafungin (N=12)			Active Control (N=5)			Total (N=17)		
	Subjects		Events	Subjects		Events	Subjects		Events
System Organ Class Preferred Term	**N**	**(%)**	**N**	**N**	**(%)**	**N**	**N**	**(%)**	**N**
General disorders and administration site conditions	**3**	**(25.0%)**	**3**	**3**	**(60.0%)**	**3**	**6**	**(35.3%)**	**6**
Chest pain	2	(16.7%)	2	0		0	2	(11.8%)	2
Gravitational oedema	0		0	1	(20.0%)	1	1	(5.9%)	1
Multi-organ failure	0		0	1	(20.0%)	1	1	(5.9%)	1
Oedema peripheral	1	(8.3%)	1	0		0	1	(5.9%)	1
Pyrexia	0		0	1	(20.0%)	1	1	(5.9%)	1
Infections and infestations	**2**	**16.7%)**	**3**	**3**	**(60.0%)**	**3**	**5**	**29.4%)**	**6**
Sepsis NOS	0		0	2	(40.0%)	2	2	(11.8%)	2
Bronchopulmonary aspergillosis	1	(8.3%)	1	0		0	1	(5.9%)	1
Enterobacter sepsis	1	(8.3%)	1	0		0	1	(5.9%)	1
Oesophageal candidiasis	1	(8.3%)	1	0		0	1	(5.9%)	1
Septic shock	0		0	1	(20.0%)	1	1	(5.9%)	1
Investigations	**2**	**(16.7%)**	**2**	**2**	**(40.0%)**	**9**	**4**	**23.5%)**	**11**
Protein total abnormal	1	(8.3%)	1	1	(20.0%)	1	2	(11.8%)	2
Alanine aminotransferase increased	0		0	1	(20.0%)	1	1	(5.9%)	1
Aspartate aminotransferase increased	0		0	1	(20.0%)	1	1	(5.9%)	1
Blood albumin decreased	0		0	1	(20.0%)	1	1	(5.9%)	1
Blood alkaline phosphatase NOS increased	0		0	1	(20.0%)	1	1	(5.9%)	1
Blood bilirubin increased	0		0	1	(20.0%)	1	1	(5.9%)	1
Blood creatinine decreased	0		0	1	(20.0%)	1	1	(5.9%)	1
Blood lactate dehydrogenase increased	0		0	1	(20.0%)	2	1	(5.9%)	2
Oxygen saturation decreased	1	(8.3%)	1	0		0	1	(5.9%)	1
Respiratory, thoracic and mediastinal disorders	**2**	**(16.7%)**	**2**	**2**	**40.0%)**	**3**	**4**	**(23.5%)**	**5**
Cough	0		0	1	(20.0%)	1	1	(5.9%)	1
Dyspnoea NOS	1	(8.3%)	1	0		0	1	(5.9%)	1
Pharyngitis	0		0	1	(20.0%)	1	1	(5.9%)	1
Respiratory distress	0		0	1	(20.0%)	1	1	(5.9%)	1
Respiratory failure	1	(8.3%)	1	0		0	1	(5.9%)	1
Metabolism and nutrition disorders	**1**	**(8.3%)**	**2**	**2**	**(40.0%)**	**4**	**3**	**(17.6%)**	**6**
Hypomagnesaemia	1	(8.3%)	2	1	(20.0%)	1	2	(11.8%)	3
Hypermagnesaemia	0		0	1	(20.0%)	1	1	(5.9%)	1
Hypochloraemia	0		0	1	(20.0%)	1	1	(5.9%)	1
Hypokalaemia	0		0	1	(20.0%)	1	1	(5.9%)	1
Vascular disorders	**2**	**(16.7%)**	**2**	**1**	**(20.0%)**	**1**	**3**	**(17.6%)**	**3**
Hypertension NOS	0		0	1	(20.0%)	1	1	(5.9%)	1
Hypertension aggravated	1	(8.3%)	1	0		0	1	(5.9%)	1
Hypotension NOS	1	(8.3%)	1	0		0	1	(5.9%)	1
Hepatobiliary disorders	**1**	**(8.3%)**	**1**	**1**	**(20.0%)**	**1**	**2**	**(11.8%)**	**2**
Cholestasis	0		0	1	(20.0%)	1	1	(5.9%)	1
Hyperbilirubinaemia	1	(8.3%)	1	0		0	1	(5.9%)	1
Renal and urinary disorders	**2**	**16.7%)**	**3**	**0**		**0**	**2**	**11.8%)**	**3**
Dysuria	1	(8.3%)	1	0		0	1	(5.9%)	1
Haematuria	1	(8.3%)	1	0		0	1	(5.9%)	1
Renal failure aggravated	1	(8.3%)	1	0		0	1	(5.9%)	1
Cardiac disorders	**0**		**0**	**1**	**(20.0%)**	**1**	**1**	**(5.9%)**	**1**
Tachycardia NOS	0		0	1	(20.0%)	1	1	(5.9%)	1
Eye disorders	**1**	**(8.3%)**	**1**	**0**		**0**	**1**	**(5.9%)**	**1**
Conjunctivitis	1	(8.3%)	1	0		0	1	(5.9%)	1

Adverse events	Micafungin (N=12)			Active Control (N=5)			Total (N=17)		
	Subjects		Events	Subjects		Events	Subjects		Events
System Organ Class Preferred Term	**N**	**(%)**	**N**	**N**	**(%)**	**N**	**N**	**(%)**	**N**
Musculoskeletal and connective tissue disorders	**1**	**(8.3%)**	**1**	**0**		**0**	**1**	**(5.9%)**	**1**
Musculoskeletal pain	1	(8.3%)	1	0		0	1	(5.9%)	1
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	**1**	**(8.3%)**	**1**	**0**		**0**	**1**	**(5.9%)**	**1**
Leukaemia NOS	1	(8.3%)	1	0		0	1	(5.9%)	1
Nervous system disorders	**0**		**0**	**1**	**(20.0%)**	**1**	**1**	**(5.9%)**	**1**
Headache NOS	0		0	1	(20.0%)	1	1	(5.9%)	1
Skin and subcutaneous tissue disorders	**1**	**(8.3%)**	**1**	**0**		**0**	**1**	**(5.9%)**	**1**
Pruritus generalized	1	(8.3%)	1	0		0	1	(5.9%)	1

Source: Table 12.6.1.2.
FAS: full analysis set; NOS: not otherwise specified.
Within a system organ class, subjects may have reported more than one type of adverse event. An adverse event observed after starting administration of the test drug/comparative drug is called "treatment emergent adverse event".

Laboratory:
Hematology parameters, such as platelets, white blood cells, neutrophils and lymphocytes were elevated in incidental cases during or after treatment. Liver enzyme parameters showed in a few subjects incidental high values in both groups. No important changes in the other standard examinations were observed.

Overview of individual subjects:
Mean values are less relevant in case of small number of subjects, therefore an overview of treatment duration, SAE incidence and death, and overall result per subject at the end of treatment are presented in Table 15. The outcome of the overall treatment success is identical for the protocol and new IDRB defined criteria.

Table 15: Overview of treatment duration, SAE incidence and death, and overall result per subject

Subject nr.	Treatment	Treat-ment duration (days)	Start SAE (days after start treat-ment)	Death (days after 1st dose)	End of study (days after start treat-ment)	Type of SAE (days after start treatment)	IDRB overall treatment success at EoT
[redacted]	**Micafungin**	34	113	113	-	-Acute myeloid leukaemia aggravated‡ (113)	No
[redacted]	**Micafungin**	29	-	-	117	-	Yes
[redacted]	**Micafungin**	26	-	-	110	-	No

Subject nr.	Treatment	Treat-ment duration (days)	Start SAE (days after start treat-ment)	Death (days after 1st dose)	End of study (days after start treat-ment)	Type of SAE (days after start treatment)	IDRB overall treatment success at EoT
[redacted]	**Micafungin**	25	24, 26/38, 33, 45	45	39	-Oesophageal candidiasis (24) -Melaena (26/38) -Bacterial sepsis (33) -Anemia NOS aggravated‡ (45) -Thrombo-cytopenia aggravated ‡ (45)	No
[redacted]	**Micafungin**	24	48	-	106	-Pneumonia aggravated (48)	Yes
[redacted]	**Micafungin**	10	11	12	-	-Dyspnea NOS‡ (11)	No
[redacted]$	**Micafungin**	10	-	-	94	-	No
[redacted]	**Micafungin**	8	24, 25, 26	26	-	-Septic shock‡ (24) -Respiratory failure (25) -Oxygen saturation decreased (26)	No
[redacted]	**Micafungin**	8	19, 35, 45, 125	-	94	-Nausea/vomiting NOS (19) -bronchitis viral (35, 125) -Cough/pyrexia/ vomiting NOS (45)	Yes
[redacted]	**Micafungin**	7	7, 11	13	-	-Leukaemia NOS‡ (7) -Dyspnea NOS (11)	No
[redacted]	**Micafungin**	5	6	6	-	-Respiratory failure‡ (6) -Oxygen saturation decreased (6)	No
[redacted]	**Micafungin**	4	5	5	-	-Broncho-pulmonary aspergillosis‡ (5)	No

Subject nr.	Treatment	Treat-ment duration (days)	Start SAE (days after start treat-ment)	Death (days after 1st dose)	End of study (days after start treat-ment)	Type of SAE (days after start treatment)	IDRB overall treatment success at EoT
[redacted]	**Caspofungin**	64	3, 48, 73	76	-	-Sepsis NOS (3) -Abdominal pain NOS (48) -Broncho-pneumonia NOS‡ (73)	Yes
[redacted]	**Caspofungin**	34	-	-	119	-	Yes
[redacted]	**Caspofungin**	18	11, 22	40	-	-Pyrexia (11) -Leukaemia NOS‡ (22)	Yes
[redacted]	**Caspofungin**	11	8, 11, 12	12	-	-Sepsis NOS (8) -Cholestasis†(11) -Multi-organ failure‡ (12)	No
[redacted]	**Voriconazole**	10	10, 11	11	-	-Septic shock‡ (10) -Respiratory distress (11)	No

Source: Listings 13.2.1, 13.2.3, 13.2.5.1, 13.2.6.2 and 13.2.7.2.
The days after first dose for subjects who died are reported only in the Death column, and are not repeated in the end of study column.
† None of the SAEs are treatment related except for cholestasis intrahepatic: possible related.
$ [redacted] in Spain with one subject is different from [redacted] in Czech Republic with 3 subjects.
‡ SAE leading to death.
IDRB: Independent Data Review Board.
NOS: not otherwise specified.
Type of SAE according MedDRA 5.0.

CONCLUSIONS:
Standard clinical practice changed from monotherapy to combination therapy, which was contrary to the inclusion criteria requiring monotherapy. This led to low enrollment (n=17) in 28 months and the study was stopped prematurely.
Efficacy conclusion: three out of 12 subjects in the micafungin group and three out of five subjects in the active control group in the overall results were rated as successful at the end of treatment by the IDRB.
Safety conclusion: In total 11 subjects died during the study: five during treatment (three in micafungin group [25%] and two in the active control group [40%]) and six in the post-treatment period (four in the micafungin group [33.3%] and two in the active control group [40%]). Infections, and respiratory, blood and general d;isorders were the causes of death. Six subjects (five treated with micafungin) completed the study.
No clear trends in efficacy and safety can be given due to the small size of the study population.

Date of Report: 1 October 2010